## REMARKS

The Applicants address the Examiner's rejections in the order he presents them in the Office Action.

The rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 16, 18, 21-23, 26, 28, and 30 under § 112, second paragraph, arguing that the term "substantially identical" recited in those claims renders them indefinite. The Examiner also rejected the claims that depend from those claims.

The Applicants have amended claims 16, 18, 21-23, 26, 28, and 30 such that they no longer recite the term "substantially identical," thus mooting the Examiner's rejection. The Applicants respectfully request, therefore, that he withdraw it.

The rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1-25 under § 102(b), arguing that U.S. Patent No. 6,506,399 (the " '399 patent") anticipates them. The Applicants respectfully disagree.

The '399 patent does not disclose all of the limitations of the claims, a biodegradable neurotoxin implant comprising 1) a neurotoxin component associated and 2) an acidity regulating component for establishing in vivo a pH in the vicinity of the neurotoxin component of less than about 7. The '399 patent does not expressly disclose the second element, an acidity regulating component, and the Examiner admits as much. The Examiner argues that the '399 patent inherently discloses this limitation, instead:

> Donovan [the '399 reference] further teaches that the ratio of different monomers such as lactide and glycolide comprising [sic] a polymer . . . While the reference of Donovan *et al.* [sic.] does not specifically teach the pH regulation caused by the monomer the property is inherent to the monomers of the lactide and glycolide used.

There is no evidence, however, that the monomers of the '399 patent inherently meet the limitation of "establishing in vivo a pH in the vicinity of the neurotoxin component of less than about 7" – and, in fact, the '399 patent suggests that the monomers do no such thing.

For there to be anticipation by inherency, the "evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D 1746, 1749 (Fed. Cir. 1991). Moreover, "inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (CCPA 1981). The burden is on the Examiner, therefore, to clearly show that the implant of the '399 patent would necessarily establish in vivo a pH in the vicinity of the neurotoxin component of less than about 7. *See In Re Glaug*, 283 F.3d 1335, 62 U.S.P.Q.2d 1151, 1152 (Fed. Cir. 2002) ("the PTO bears the initial burden of presenting a prima facie case of unpatentability. If the PTO fails to meet this burden, then the applicant is entitled to the patent.").

The Applicants respectfully submit that the Examiner has not met his burden. The Examiner cites only to column 25, lines 16-22 of the '399 patent, but this passage discusses modifying the pH of the process used to form a finished implant – it says nothing about modifying pH of the implant itself, or of the environment in which it is implanted:

> By altering the properties of a biodegradable polymer, the contributions of diffusion and/or polymer degradation to neurotoxin release can be controlled. For example, increasing the glycolide content of a poly(lactide-co-glycolide) polymer and decreasing the molecular weight of the polymer can enhance the hydrolysis of the polymer and thus, provides an increased neurotoxin release from polymer erosion. In addition, the rate of polymer hydrolysis is increased in non-neutral pH's.

> Therefore, an acidic or a basic excipient can be added to the polymer solution, used to form the microsphere, to alter the polymer erosion rate.

Col. 25., lns. 27-37. The "acidic or basic excipient" is "used to form the microsphere," an embodiment of the implant. This is consistent with the examples the patent provides for making the implant. *See, e.g.,* col. 15, lns. 10-20 ("A method for making an implant . . . can have the steps of: dissolving a polymer in a solvent to form a polymer solution; mixing or dispersing a botulinum toxin in the polymer solution . . . and allowing the polymer-botulinum toxin mixture to set or cure"), and col. 28, lns. 32-47. The Examiner provides no evidence that the implant the '399 patent describes would establish in vivo a pH in the vicinity of the neurotoxin component of less than about 7. The Applicants respectfully request, therefore, that the Examiner withdraw the rejection under § 102(b).

The rejection under § 102

The Examiner rejected claims 1, 16-23, and 25-33 under § 102, arguing that U.S. Patent No. 6,312,708 (the " '708 patent") anticipates them. The Examiner does not identify the provision under § 102 on which he basis his rejection, but, under any provision of that section, the Applicants respectfully disagree that the rejection is proper.

The '399 patent, which the Examiner argued anticipated all of the claims under § 102(b), is a continuation of the application that led to the '708 patent. The Examiner now argues that the '708 patent anticipates claims 1, 16-23, and 25-33. The specifications of the '399 and '708 patents appear to be identical, and, again, the Examiner relies on the argument that "the acidity-regulating component is an inherent property of the polymers used in the biodegradable implant of the present invention." The Applicants address this argument in the previous section of this paper, and respectfully request that the Examiner withdraw the § 102 rejection for the reasons the Applicants state there.

The first rejection under § 103

The Examiner rejected claims 1 and 26-30 under § 103, arguing that the claims are obvious in view of the '399 patent when considered in combination with U.S. Patent No. 5,741,329 (the "Agrawal reference"). The Applicants respectfully disagree.

The Examiner states that "the alkaline lability of the neurotoxin is an obvious motivation for a pH-regulating component." Office Action, at 6. Yet the Agrawal reference provides no solution for one skilled in the art who, confronted with the problem the Examiner alleges, seeks a solution. In the implant of the presently claimed invention the acidity regulating component establishes in vivo a pH in the vicinity of the neurotoxin component of less than about 7, that is, an acidic pH. The Agrawal reference, in contrast, describes an acidic pH as a *problem* – it does not suggest, therefore, a solution that would lead one to the implant of the present invention.

The Agrawal reference seeks to maintain a constant pH, and not create shuift the pH to an acidic one as the claimed invention requires: "Solving the problem of controlling pH shifts due to polymer breakdown products would improve the biocompatibility of a variety of implantable devices for both short term and long term use in the medical industry." Agrawal reference, col. 1, lns. 64 – 67. Hence, the reference states that

> Another aspect of the invention provides a method for minimizing tissue damage related to adverse pH changes from the presence of polymer breakdown products. . . Potential changes in pH, such as from increases in acidity related to break down of polylactic or polyglycolic acid, may thus be offset by the release of an alkaline substance included with the polymer.

Col. 2, lns. 43-54.

Later the reference states that

> Many of the problems associated with shifts in pH due to biodegradable polymer breakdown products are in part remedied by the compositions and methods of the present invention. The inventors have found that the inclusion of a pH regulating substance, such as an alkaline substance, an acidic substance, or a buffering agent, included with the biodegradable polymer, will hinder shifts in pH that typically occur as the polymer breaks down. . . This technique will also guard against a variety of pH-related in vivo side effects associated with pH shifts at implantation sites.

Col. 2, lns. 8-23. The Agrawal reference also refers to acidic pH as a problem; hence, it states, for example, that:

> Preferably, the selected pH controlling substances are of an alkaline nature, and are included with polymers that render relatively acidic polymeric breakdown products. . . Because decreases in pH surrounding biodegradable polymeric devices, such as those comprised of polyglycolic acid and polylactic acid, have been associated with adverse tissue responses, the present invention may also be employed for minimizing these adverse responses

Col. 5, lns. 9-11 and lns. 22-26.

Whereas the implants of the Agrawal reference seek to minimize pH shifts, the claimed implants seek to *induce* a shift to an acidic pH. For this reason, the Agrawal reference does not render the claimed implants obvious.

Moreover, Agrawal does not disclose or suggest any acidity regulating components comprising monomers and oligomers derived from the same biodegradable polymer, such as is claimed in claims 16, 18, 21, 23, 26, and 30.

For the foregoing reasons, the Applicants respectfully request that the Examiner withdraw the first rejection under § 103.

The second rejection under § 103

The Examiner rejected claims 1 and 11-13 under § 103, arguing that the claims are obvious in view of the '399 patent when considered in combination with U.S. Patent No. 6,440,460 (the "Gurney reference"). The Applicants respectfully disagree.

The Gurney reference discloses a polymer composition that, as the Examiner points out, causes a steady decrease in pH:

> Upon progressive hydrolysis of the ortho ester polymers, an increasing amount of carboxylic acids R.sub.1 COOH is being liberated. This causes a decrease of the pH-level in-vitro from values of about 6.5 to 4.5 to even lower values in 1-5 days depending on the moleclur weight of the polymer.

Col. 1, lns. 61-67. As with the Agrawal reference, this decreasing pH is a problem:

> This decreasing pH-level renders pharmaceutical compositions or administration systems containing the above-mentioned carboxylic acid ester ortho ester polymers less feasible for various types of administration, especially intramuscular, subcutaneous and intraocular administration, since it has firmly been established that the injection of a formulation with an acidic pH could trigger inflammation.

Col. 2, lns. 1-8. Hence, the Gurney reference does not seek to maintain an acidic pH, but to buffer the pH to maintain it at physiologically acceptable levels:

> This problem has been solved by adding a pharmaceutically acceptable salt of an acid, which together with the acid being liberated from the decomposition of the carboxylic acid ortho ester polymer (I) forms a buffer system in a physiologically acceptable pH-range.

Col. 2, 23-28.

The Gurney reference is thus distinguishable for the same reasons as the Argawal reference: the point of the acidity regulating component is to maintain an acidic pH; the point of the Gurney reference is to *avoid* an acidic pH ("since it has

firmly been established that the injection of a formulation with an acidic pH could trigger inflammation."). For the foregoing reasons, the Gurney reference does not render any of the claims obvious, and the Applicants respectfully reuest that the Examiner withdraw the rejection under § 103.

The undersigned authorizes the Director to charge any fees required or necessary for the filing, processing or entering of this paper or any of the papers transmitted with it, and to refund any overpayment, to deposit account 01-0885.

Respectfully submitted,

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